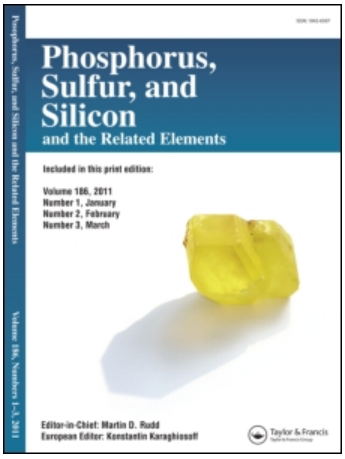

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NOVEL BISPHOSPHONATES FOR CALCIUM-RELATED DISORDERS

Gershon Golomb, Joel M. Van Gelder, Ivan S. Alferiev, Asher Ornoy, Amnon Hoffman, Ada Schlossman, Aviva Friedman-Ezra, Naama El-Hanany-Rozen, Ravit Chen, Vered Solomon, Hagit Cohen, Laura Rabinovich and Eli Breuer
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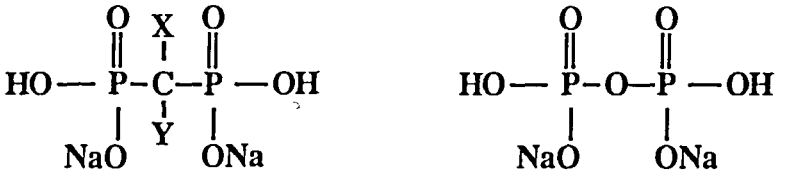
Abstract Bisphosphonates are drugs used clinically in various calcium-related disorders such as Paget's disease, hypercalcemia of malignancy, and tumor osteolysis and are undergoing clinical trials for osteoporosis. From the results obtained in various clinical studies using conventional bisphosphonates, it appears that there is a need for compounds with a greater margin between the inhibition of bone resorption and the inhibition of mineralization, without an accompanying increase in toxicity, and at the same time, improved oral bioavailability without gastrointestinal side effects. One research strategy to address these problems is the synthesis and evaluation of non-geminal bisphosphonates, bisacylphosphonates. It is concluded that a new generation of calcium-binding compounds with antiresorptive and anticalcification properties have been obtained. In comparison to clinically used bisphosphonates, the new compounds possess very low toxicity and improved bioavailability.

Key Words: Bisphosphonates, calcium-related disorders, osteoporosis, calcium, calcification, hypercalcemia

INTRODUCTION

Bisphosphonates are a class of drugs developed about 25 years ago that can be considered stable analogs of pyrophosphate (P-O-P), a physiological regulator of calcification and bone resorption [1]. They are characterized by a non-hydrolyzable P-C-P bond. All bisphosphonates (BP's) are disodium salts of the tetraacids with a molecular weight of ~250 daltons, see Figure:

Geminal bisphosphonate Pyrophosphate



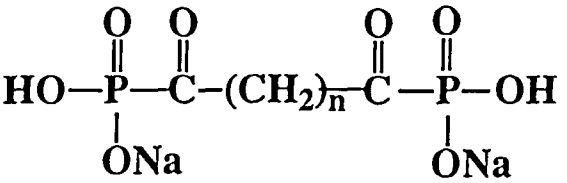
X = OH, Y = CH_3, Etidronate
X = Cl, Y = Cl, Clodronate
X = OH, Y = $(CH_2)_2$ - NH_2, Pamidronate
X = OH, Y = $(CH_2)_3$ - NH_2, Alendronate

A number of such geminal BP's have been approved for clinical use in Paget's disease and hypercalcemia of malignancy, and recently for clinical use in osteoporosis [2, 3, 4, 5]. BP's, like other bone seeking agents, are irreversibly trapped with calcium in sites of new bone formation, a property that underlies their use as bone scanning agents. However, their precise cellular and biochemical mechanisms of action are not fully understood. The inhibitory effect of BP on bone resorption has principally been attributed to a direct action on osteoclasts [6] or to an indirect action through the mediation of osteoblasts. [7] The pharmacologic basis for structure-related differences in potency among the BP's is not completely understood, but it is evident that BP's with an amino group in the side chain or in a heterocyclic ring are the most potent *in vivo*. It is expected that different modes of activity i.e., inhibition of resorption and/or mineralization, and toxic effects are dependent on the structure of the functional groups [8]. An initial requirement for BP's activity is the binding of the compound through its oxygens to bone's hydroxyapatite (HAP) enabling localized pharmacologically active concentrations in the bone [9] . It was postulated that the side-chain of a geminal bisphosphonate is of critical importance for the cellular activity.

RESULTS and DISCUSSION

It had been believed that non-geminal BP's P-$(C)_n$-P with $n \geq 2$ were inactive [1]. However, we found recently [10, 11, 12, 13] that non-geminal BP's with hydroxyimino and especially with keto groups at α positions relative to the

phosphonic groups are active as anticalcification and antiresorption agents (see structures below).



n = 4, AdBP; n = 5, PiBP
n = 6, SuBP; n = 7, AzBP
n = 8, SeBP; n = 10, DoBP

Several *in vitro* and *in vivo*, experimental models were utilized in order to characterize the activity of bisacylphosphonates: 1) inhibition of hydroxyapatite (HAP) formation, 2) inhibition of HAP dissolution, 3) inhibition of the pathological calcification of bioprosthetic tissue implanted subdermally in rats, 4) inhibition of bone resorption in rats, 5) toxicity studies, and 6) bioavailability and disposition. In the models of HAP formation (pH-stat, stable and metastable solutions of calcium-phosphate) pamidronate is more active than AdBP, the most potent bisacylphosphonate, as well as other bisacylphosphonates with longer alkyl chains [13]. In the model of inhibition of HAP dissolution AdBP has comparable activity to that of pamidronate, while the other bisacylphosphonates are inferior. This ranking of activity correlates with the moderate antiresorptive activity of bisacylphosphonates, exhibited in the young intact rat model [8, 13]. The bisacylphosphonates were found highly active in inhibiting the calcification of bioprosthetic tissue implanted subdermally in rats [10, 11, 13]. Tissue calcification was completely inhibited by AdBP, PiBP, SuBP and pamidronate.

Structure-activity-relationship studies revealed that the keto groups in α positions to the phosphonic functions render activity. The BP's with shorter alkyl chains are highly active in the various models studied. General requirements for activity in both geminal- and non-geminal BP's are 2 phosphonic functions (1 or 4 are inferior), and activity was exhibited only when at least three ionizable groups are present in the molecule (the diesters were inactive). Finally, the calcium salt/complexes of bisacylphosphonates are more soluble than the corresponding geminal BP's. This unique characteristics probably responsible for the improved oral bioavailability of bisacylphosphonates, 10 to 20 times higher than that of geminal BP's [14, 15].

CONCLUSION

It appears that there is still a need for compounds with a greater margin between bone resorption inhibitory activity and that of mineralization, without an accompanying increase in toxicity, and at the same time, improved oral bioavailability without gastrointestinal side effects.

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